REMARKS

Claims 245-251 are pending in the above-referenced application. As will be discussed in further detail below, claims 245, 247-251 have been amended to more distinctly claim that which Applicants regard as their invention. Specifically in claim 245, "a cell" is replaced with "one or more cells". This claim amendment is supported by the specification since "a cell" and "cells" are used interchangeably throughout the specification and "a" in claim language is commonly interpreted to mean "one or more". Additionallly inclaim 245 "non-native processing element" is replaced with "non-native intron". Claim 246 is cancelled. No new matter has been added. Claim 252 has been added to recite a specific embodiment. It is supported by the specification.

Formal drawings and an Information Disclosure Statement will be submitted in a supplemental response.

The Rejection Under 35 U.S.C. 112, First Paragraph (Written Description)

Claims 245-251 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, the Office Action states on pages 8-9:

> The claims lack written description since a representative number of species of the constructs claimed (and specifically the embodiments elected as species) for use in a cell are not adequately described by the specification as filed. ...Although, the specification as filed has shown (in the figures especially), numerous vector-like constructs, the only species of an intron containing construct for expression of an antisense is that of the U1 cassette construct with antisense to HIV expressed therefrom in a cell in cell culture. One of skill in the art would not have recognized that applicant was in possession a representative number of other species of the broad genus of

> constructs claimed having other intron segments which are processed away from the antisense, nor having other antisense with a known antisense function. In regards to the breadth of antisense claimed, design of an antisense is based on knowledge of the target gene nucleic acid structure. One of ordinary skill in the art would not have recognized that applicant was in possession of a representative number of species of antisense (or ribozyme) to any target gene from the teachings of the specification as filed. Thus, absent further specific (not general) guidance for the nucleic acid structure of other introns useful as non-native processing elements (note that the information is also needed as to which cells or cell types (tissues), are compatible with the particular intron used), as well as specific guidance for antisense to other target genes (or the specific target use sequence from which to design the antisense) would have been necessary for one of skill in the art to immediately envisage other representative species of the claimed genus of constructs useful in the claimed cells. Furthermore, neither the specification nor the prior art taught a representative number of species of the claimed constructs having the function of use in cells in a whole organism, via administration either *in vivo* or *ex vivo*. The examples in the instant specification as filed do not teach the direct correlation between any such vector constructs (including the U1-anti-HIV constructs) as having a specific function in a cell in a whole organism.

Applicants respectfully traverse the rejection. It is Applicants position that the constructs used in the method of the present invention as well as the method itself are adequately described. Figures 27-31 and 47 clearly describe obtaining the construct used in the method of the present invention. The MPEP in section §2163 II.A.3. (a) states:

> An applicant may show possession of an invention by disclosure of drawings or structural chemical formulas that are sufficiently detailed to show that applicant was in possession of the claimed invention as a whole..... The description need only describe in detail that which is new or not conventional..... This is equally true whether the claimed invention is directed to a product or a process.

Figures 27-31 and 47 are sufficiently detailed and meet the criteria set forth in the MPEP. The stick figures presented in the figures were certainly

standard for figures presented by those of ordinary skill of the art to describe a construct or composition. A specification may, within the meaning of 35 U.S.C. 112, first paragraph, contain a written description of a broadly claimed invention without describing all species that the claim encompasses. Representative samples are not required by the statute and are not an end in themselves. *Amgen, Incorporated v. Chugai Pharmaceutical Company, Limited,* 18 USPQ2d 1016, 1027 (Fed. Cir. 1991). It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. *Ex parte Obukowicz,* 27 USPQ2d 1063 (BPAI 1993).

Applicants assert that a representative number of species have been disclosed. Certainly specific embodiments were set forth in Example 19. Example 19 discloses the expression of HIV antisense and example 29 discloses the construction of an antisense expressing multi-cassette construct containing three T7 promoters and an intron-containing T7 RNA polymerase gene. It is clearly evident that an incompatible cell would be a procaryotic cell and a compatible cell would be a eucaryotic cell. Furthermore, four specific applications are described in the specification on pages 87-88:

a) Conditional inactivation of genes when these genes would be lethal to the host cell or when present in a host cells introduce a danger;

b) Expression of polymerases (e.g., T3, T7 and SP6) in compatible cells;

c) Cloning of incompatible genes together on the same construct, eg., a single construct containing sequences for the production of T7 promoter directed transcript(s) of choice and T7 RNA polymerase

d) Interaction of a non-native gene or its protein products in a cell where the interaction of the introduced genes and/or their gene products can yield useful intracellular processes for gene therapy.

Applicants do note that claim 245 has been amended so that the construct used in the present invention comprises **non-native introns**. It is Applicants' position that any intron would potentially be useful in the construct used in the present invention. As stated in the specification on page 83, first paragraph the construct comprises a **non-native processing element** that is **substantially removed during processing in a compatible cell.** Furthermore, the specification states on page 84, first paragraph

> The present invention provides a **universal method for utilizing processing elements**, including heterologous elements, for conditional gene inactivation. Rather than a restriction enzyme site, the frequently occurring sequence (C/A)AGG post splice junction sequence is used as the insertion site. This site results from the consensus sequence resulting from an excision of an intron. The consensus splice sequence for splice donors is (C/A)AG*GU and the consensus sequence for splice acceptors $(U/C)_nN(C/U)AG*G$ where * represents the splice site (Reference omitted). The frequent occurrence of this sequence provides numerous potential sites for the insertion of processing elements. Insertion at any of these sites in a gene coding region should not affect subsequent removal of the processing element in a compatible cell.....

On page 85, first paragraph of the specification, it is noted that a restriction fragment of DNA containing the beta-globin intron with the conserved bases of the 3' end of the donor exon attached, could be introduced into various sites of a cDNA copy of beta-globin and subsequently spliced out normally, irrespective of the intron location in the beta-globin coding sequence. This finding is further evidence that the particular sequence of the intron is of little consequence. The intron and its flanking sequence contain the necessary

and sufficient sequence information for splicing out the intron regardless of the neighboring sequences.

Applicants' position is further supported in Lewin, 1994, Genes V,Oxford University Press, pages 914-915, attached hereto as Exhibit A (hereinafter "Lewin"). Lewin in the last paragraph of page 914 states:

> Experiments to construct hybrid RNA precursors show that any 5' splicing site can in principle be connected to any 3' splicing site. For example, when the first exon of the early SV40 transcription unit is linked to the third exon of mouse β-globin, the hybrid intron can be spliced out to generate a perfect connection between the SV40 exon and the β-globin exon....

Lewin in the first paragraph of page 915 concludes:

> Splicing sites are **generic:** they do not have specificity for individual RNA precursors and individual precursor **do not** convey specific information (such as secondary structure) that is need for splicing.

Clearly, there is no such thing as a β-globin specific splicing system or an SV40 splicing specific system. Instead, the splicing out of introns makes use of a universal cellular system that is capable of splicing out of thousands of different introns within a cell.

Furthermore, the type of compatible cells used in the method of the present invention is also not a critical feature. Applicants position is again supported by Lewin on page 915, second paragraph:

> And the apparatus for splicing is not tissue specific; an RNA can usually be properly spliced by any cell, whether or not it is usually synthesized in that cell.

Clearly, the type of introns to be used, the nucleic acid products expressed and cells to be used in the method of the present invention are non-critical features of the invention and thus require no written support. A description need not be provided for features that are not essential or critical

to the invention. *Ethicon Endo-Surgery, Inc. v. United States Surgical Corporation, 93 F. 3*d 1572 (Fed. Cir. 1996). An inventor need not explain every detail since he is speaking to those skilled in the art. What is conventional knowledge will be read into the disclosure. *In re Howarth*, 654 F.2d 103, 210 USPQ 689 (CCPA 1981).

In view of the above arguments, Applicants assert that the rejection has been overcome. Applicants therefore request that the rejection under 35 U.S.C. 112, first paragraph (written description) be withdrawn.

The Rejection Under 35 U.S.C. §112, First Paragraph (Enablement)

Claims 245-251 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of selectively expressing a nucleic acid product in a cell in cell culture (in vitro), does not reasonably provide enablement for methods of expressing the nucleic acids in a whole organism (in vivo). In the Examiner's view, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. It is specifically asserted that the claimed invention is directed to the expression of antisense and/or ribozymes from vectors having a non-native processing element in a cell, yet in the Examiner's view, no such antisense or ribozyme constructs were taught in the specification as filed as reduced to practice for expression of the claimed constructs in cells in a whole organism.

The Examiner further asserts that there is a high level of unpredictability known in the antisense and relative ribozyme art for *in vivo* (whole organism) applications. A number of references are cited. It is conceded that these references primarily refer to the unpredictability of administration of antisense oligonucleotides,

but may also be applied to antisense expressed from a vector since the function of the antisense is the same, to locate and bind a target gene, thereby decreasing its expression.

It is further asserted on page 16, lines 7-18

> One of skill in the art would not accept on its face the successful delivery of the disclosed antisense molecule constructs *in vivo* and further, treatment effects, in view of the lack of guidance in the specification and the unpredictability in the art. Neither the specification nor technology today teach general guidelines for successful delivery or treatment effects of antisense molecules in whole organisms. Specifically the specification does not teach (1) stability of the antisense molecule constructs *in vivo* (2) effective delivery to the whole organism and specificity to the target tissues, (3) dosage and toxicity, nor (4) entry of molecule into cell and effective action therein marked by visualization of the desired treatment effects. These key factors are those found to be highly unpredictable in the art as discussed *supra.* The lack of guidance in the specification as filed for these factors would therefore require "trial and error" experimentation beyond which is taught by the specification as filed. Therefore, it would require undue experimentation to practice the invention as claimed.

It is concluded in the paragraph bridging page 20, lines 5-10:

> The above rejection does not imply that an animal model of disease is needed to enable the instantly claimed invention. The rejection is centered on the ability to make and use the claimed methods with any expression construct as claimed, and the position has been maintained, based on the references cited, that there is a high level of unpredictability in the art of design and use of antisense in a whole organism. Although applicants state that clinical trials are underway, the information in Exhibit 3 does not teach what constructs are in trials and whether or not they function as instantly claimed in the context of a whole organism.

Applicants respectfully traverse the rejection. First, *contra* to assertions made in the Office Action, antisense constructs to be used in the method of the present invention were certainly disclosed in the instant specification. As noted

above, Example 19 discloses the synthesis of a eukaryotic vector that expresses T7 RNA as well as antisense sequences (antisense to the 5' common leader, the coding sequence for Tat/Rev and the splice acceptor site for Tat/Rev, directed by a T7 polymerase. The procedure used for obtaining the construct is shown in Figures 24-31. Example 29 and figure 47 discloses the construction of an antisense expressing multi-cassette construct containing three T7 RNA promoters and an intron-containing T7 RNA polymerase gene.

Second, Applicants assert that methods were well known in the art for obtaining stable antisense molecule constructs and methods for their delivery into cells. Examples are provided in Exhibit B:

1. Wang et al., 1995, "Delivery of antisense oligodeoxyribonucleotides against the human epidermal growth factor receptor into cultured KB cells with liposomes conjugated to folate via polyethylene glycol", Proc. Natl. Acad. Sci. USA 92:3318-3322;
2. Vlassov et al., 1993, "Penetration of oligonucleotides into mouse organism through mucosa and skin", FEBS Lett. 327:271-274;
3. Agarwal et al., 1995, "Absorption, Tissue Distribution and In Vivo Stability in Rates of a Hybrid Antisense Oligonucleotide Following Oral Administration", Biochem. Pharmacol. 50:571-576;
4. Rossi, 1995, "Controlled, targeted, intracellular expression of ribozymes: progress and problems", Trends Biotechnol. 13:301-306.

Applicants note that the law does not require a specification to be a blueprint in order to satisfy the requirement for enablement under 35 USC 112, first paragraph. Not every last detail is to be described, else patent specifications would turn into production specifications, which they were never intended to be. *Staehlin*

v. Secher 24 USPQ2d 1513, 1516 (BPAI 1992). The law does not require an applicant to describe in his specification every conceivable embodiment of the invention. *U.S. v. Telectronics, Inc.*, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988).

Furthermore, it is Applicants position that it would not require undue experimentation to go from the *in vitro* studies to *in vivo* studies. First, *contra* to assertions made in the Office Action, it is not so unpredictable that t a nucleic acid construct containing a non-native processing element and produces a nucleic acid product that may be an antisense, sense or protein binding nucleic acid sequence or ribozyme would be effective in vivo. The Office Action cites a number of references purporting to illustrate the unpredictability of antisense technology. However, as noted in the Office Action, the references cited all concern the use of antisense oligonucleotides **not** constructs containing antisense sequences. Therapeutics based on oligonucleotides offers a pharmaceutical approach whereas the use of the plasmids to generate antisense RNA inside the cell involve a gene therapy approach. The method of the present invention uses **a construct** that may produce an antisense. Applicants submit as Exhibit C, the following references showing the correlation between in vivo and in vitro results using both oligonucleotides, ribozyme, RNAi sequences and vectors containing antisense sequences:

1. Opalinska and Gewirtz, 2002, "Nucleic-acid Therapeutics: Basic Principles and Recent Applications", Nature Reviews, Drug Discovery 1:503-514 (hereinafter Opalinska and Gewirtz, 2002). Applicants note that one of the references cited by the Examiner as evidence of predictability, Jen, was coauthored by Gewirtz. However, Opalinska and Gewirtz, 2002, disclose that a number of clinical trials in Phase II/III are currently underway with antisense compounds and express optimism that these compounds will prove to be efficacious.

2. Stone et al., 2003, "The pain of antisense: in vivo application of antisense oligonucleotides for functional genomics in pain and analgesia", Adv. Drug Del. Rev. 55:1081-1112; (Stone et al., 2003). Specifically, Stone et al. states on page 1089, column 1, lines 31-38:

> The potential for discrepancies between in vivo and in vitro efficacies does not discount the possible benefits of selecting active ASOs in an in vitro system provided such a system is easily available, is optimized and models closely the cell types to be targeted in vivo (for example, using neuroblastoma cell lines for CNS targets)

3. Wang et al., 1999, "Antitumor activity and pharmacokinetics of a mixed-backbone antisense oligonucleotide targeted to the R1A subunit of protein kinase A after oral administration", Proc. Natl. Acad. Sci. USA 96:13989-13994 discloses a correlation between in vitro and in vivo results.
4. Voorhoeve and Agami, 2003, "Knockdown Stands Up", Trends in Biotechnology 21:2-4 reviews the correlation of in vitro and in vivo results using RNAi.
5. Vacek et al., 2003, "Antisense-mediated redirection of mRNA splicing", Cell. Mol. Life Sci. 60:825-833, discuss how therapeutics based on oligonucleotides offers a pharmaceutical approach whereas the use of the plasmids to generate antisense RNA inside the cell involve a gene therapy approach and also summarize studies conducted with both oligonucleotides and plasmids;
6. Kelley et al., 2003, :"CaSm antisense gene therapy: a novel approach for the treatment of pancreatic cancer", Anticancer Res. 23:2007-13 discloses that an adenovirus expressing antisense RNA to the CaSm gene is able to reduce endogenous CaSm mRNA expression in vitro

and extends survival in an in vivo SCID mouse model of human pancreatic cancer;

7. Xu et al., 2003, "Molecular Therapeutics of HBV", Current Gene Therapy 3: 341-355 discloses the use of antisense RNA and DNA as oligonucleotides and expressed in vectors and hammerhead ribozymes for treating HBV infection.

Applicants note that it is stated in the MPEP §2107.03 that "If reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays, or from testing in an animal model or combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process". Given that a correlation can be established between the in vitro assays and the asserted utility, in vivo studies are not necessary. Furthermore, it would not constitute undue experimentation to design and use , e.g., antisense in the whole organism.

Furthermore, it is stated in the Office Action that Claims 248 and 249 (and 245 from which they depend) are further rejected for the limitation of introducing *ex vivo* and *in vivo* the construct to "a cell." In response, Applicants first assert that the use of "a" in front of a particular claim element is synonymous with "one or more". However, in order to advance prosecution, claims 245 and 247-250 have been amended to recite that the nucleic acid product is expressed in one or more cells. Applicants do respectfully point out that the specification discloses expression of nucleic acid products in both a singular cell and a plurality of cells.

In conclusion, given that a number of embodiments of the present invention are disclosed and that methods are well known in the art for obtaining stable antisense molecule construct and methods for their delivery into cells, it is Applicants position that undue experimentation is not required to perform the

method of the present invention. Furthermore, it is not necessary to provide results from in vivo studies since results with e.g., antisense oligonucleotides or constructs expressing antisense sequences, ribozymes in published studies can be correlated with results from in vivo studies.

* * * * * * * * *

Summary and Conclusions

Claims 245-251 are presented for further examination. No further claims have been presented.

If a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney request that he be contacted at the number provided below.

Respectfully submitted,

Ronald C. Fedus
Registration No. 32,567
Attorney for Applicants

ENZO LIFE SCIENCES, INC.
c/o ENZO BIOCHEM, INC.
527 Madison Avenue, 9th Floor
New York, New York 10022
Telephone: (212) 583-0100
Facsimile: (212) 583-0150